

OBSERVATIONS

Pioglitazone-Induced Acute Rhabdomyolysis

Pioglitazone, a peroxisome proliferator-activated receptor γ agonist, is a relatively new oral antidiabetes agent. It has been shown to decrease insulin resistance in patients with type 2 diabetes, resulting in lowered blood glucose concentrations and A1C values. It can be used alone or in combination with metformin or a sulfonylurea. The adverse effects of pioglitazone include weight gain, headache, and edema.

We report here a case of a patient who developed severe acute rhabdomyolysis after receiving pioglitazone. A 52-year-old man had a 2-year history of type 2 diabetes that was treated with gliclazide (60 mg/day). Six weeks after addition for pioglitazone (15 mg/day), the patient was admitted to hospital for 4 days for myalgia and severe muscle weakness.

He had no recent viral illness or other complaints. He denied any change from his normal level of activity. No alcohol ingestion, illicit drugs, unprescribed medication use, or trauma was present.

A physical examination revealed severe proximal muscle weakness and tenderness affecting all four limbs. Laboratory tests showed marked increases in the serum creatinine phosphokinase (9,851 IU/l [normal limit 150 IU/l]), serum myoglobin, and aspartate aminotransferase (98 IU/l) levels. His creatinine serum level was normal at 60 μ mol/l. There were no signs of severe hyperglycemia, diabetic ketoacidosis, hypokalemia, or hypophosphatemia.

Autoantibody screening and viral serologies were negative. Thyroid function was normal. Electromyography studies

and a muscle biopsy were not considered to be warranted at that time. Drug-induced rhabdomyolysis was suspected, pioglitazone was stopped, and the patient underwent hydration and bicarbonate therapy.

The patient's serum creatinine phosphokinase level declined to 752 IU/l on day five after admission and returned to baseline within 4 weeks of discharge from the hospital. His muscle symptoms had also improved. His glycemia was well controlled with gliclazide and acarbose.

According to the Naranjo probability scale, pioglitazone-induced rhabdomyolysis was probable (1). This diagnosis is based on the exclusion of potential medical causes such as hypothyroidism, infection, muscle trauma, alcoholism, the patient's drug exposure, and the resolution of signs and symptoms when pioglitazone was withdrawn.

In our review of the literature and according to data from a MEDLINE search, previous case reports of elevated serum creatinine phosphokinase, myopathy, or rhabdomyolysis have been identified in patients taking rosiglitazone or troglitazone (2,3). Potential risk factors identified in these cases included concomitant therapy with fibrates, alcohol abuse, and asymptomatic mild creatinine phosphokinase elevation prior to initiating therapy.

A recent study identified no significant differences in rates of myopathic events in type 2 diabetic patients taking thiazolidinediones (rosiglitazone or pioglitazone) compared with those taking other antidiabetic agents (4). Furthermore, concomitant use of statins and thiazolidinediones was not associated with increased risk of myopathic events beyond that conferred by statins alone. Although no case reports of pioglitazone-induced severe myopathy and rhabdomyolysis were identified in our search, isolated minor elevations in serum creatinine phosphokinase levels or muscle pain were reported as an adverse effect

of this drug (5). Clinicians should be vigilant of this side effect, and a monitoring of serum creatinine phosphokinase levels in patients on pioglitazone monotherapy who developed myalgia seems to be reasonable.

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References

1. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–245
2. Kennie N, Antoniou T, Berger P. Elevated creatine kinase and myalgia in a patient taking rosiglitazone. *Ann Pharmacother* 2007;41:521–524
3. Yokoyama M, Izumiya Y, Yoshizawa M, Usuda R. Acute rhabdomyolysis associated with troglitazone. *Diabetes Care* 2000;23:421–422
4. Koro CE, Sowell MO, Stender M, Qizilbash N. The risk of myopathy associated with thiazolidinediones and statins in patients with type 2 diabetes: a nested case-control analysis. *Clin Ther* 2008;30:535–542
5. Henney JE. New type 2 diabetes drugs. *JAMA* 1999;282:932